Conclusion: Our data showed that metastasis to lymph nodes and alcohol consumption are the main factors that affect mortality in HNC patients of Tomsk region.

http://dx.doi.org/10.1016/j.ejcsup.2015.08.016

T93

Immune system contributes to the efficacy of cancer chemotherapy

N. Cherdyntseva[a,b,*], M. Stakheyeva[a], N. Litviakov[a,b], M. Zavyalova[a,b], Y. Kukharev[a], J. Kzhyshkowska[a]. [a] *Tomsk Cancer Research Institute, Tomsk, Russian Federation,* [b] *Laboratory for Translational Cellular and Molecular Biomedicine, National Research Tomsk State University, Tomsk, Russian Federation* * Corresponding author.

Background: Risk of metastasis formation is provided by both tumor cell biological characteristics and the microenvironment features within the primary tumor along with local and systemic conditions for metastatic niche formation. The inflammatory infiltration has been shown to strongly impact on tumor progression (Whiteside, 2013). Dronca et al. (2011) showed that immunosuppressive factors in the tumor microenvironment may impair not only local immune responses but also disturb systemic immunity. Zitvogel et al. anticipate that the comprehension of the mechanisms governing the immunogenicity of cell death will have a profound impact on the design of anticancer therapies.To study the impact of immune system on clinical response to neoadjuvant chemotherapy and metastasis-free survival in breast cancer patients.
Materials and methods: 350 patients with newly diagnosed invasive breast cancer treated with neoadjuvant chemotherapy (NAC) were enrolled into the study. The procedures were made in accordance with the Helsinki Declaration. Clinical response to chemotherapy, the 5-year metastasis-free survival and all major clinical and morphological parameters were determined. The original method of multidimensional data visualization was applied to present the immune system state as integral entirety in visual image for classification of patients with different risk of metastasis (NovoSpark Corporation, Canada). Copy number aberrations (CNA) of cytokine gene regions in tumor specimens were tested using high-density microarray platform CytoScanTM HD Array (Affymetrix, USA). Cytokine gene polymorphism was analyzed. Subpopulations of lymphocytes and macrophages were determined within the primary tumors by IHC.
Results: We found, that favorable clinical immediate response to preoperative chemotherapy was related to the high levels of IL-1beta, TNF-alpha and IL-10 production by peripheral mononuclear cells before the treatment. This correlation was further confirmed by data from the study on association between cytokine gene functional polymorphism and response to NAC. We used NovoSpark Corporation visualization approach allowing the representation the immune system state as integral unit and to discriminate breast cancer patients with high and low risk of haematogeneic metastasis. When estimated before cancer treatment, 95% of breast cancer patients had risk of metastasis. The neoadjuvant chemotherapy and surgical tumor removal reduced the risk of tumor progression to 62–71%. However, in a year after adjuvant chemo- and radiotherapy, the patient group with high risk of metastases increased to 81% again. Thus, the cancer treatment can change the primarily estimated outcome prognosis in breast cancer patients, and the monitoring of immune system is a promising approach to predict the risk of cancer progression or resistance to the therapy. We have found the connection between the profile of intra-tumor inflammatory elements and chemotherapy efficacy.Cytokine gene expression may be influenced by the chromosome anomalies (CNA – Copy Number Aberration) – deletion and amplification – of cytokine gene loci in tumor cells. We found the close relation between the clinical response to NAC and gain of function of IL-10 and CHI3L1 (YKL40) genes. In contrast, loss of TNF-alpha and IL-17 gene function due to corresponding CNA was associated with good response to NAC. Metastasis-free survival of breast cancer patients was shown to be closely related to CNA.
Conclusion: The parameters of the activation of systemic and intra-tumoral immune system by growing tumor and its dissemination have to be validated in order to identify the new prognostic markers for the efficiency of the neoadjuvant chemotherapy.

http://dx.doi.org/10.1016/j.ejcsup.2015.08.017

P133

DNA inhibits dsRNA-activated NF-kB-based inflammation in tumour cells: The role of Ku protein

A. Cherepanova*, V. Vlassov, P. Laktionov. *Institute of Chemical Biology and Fundamental Medicine SD RAS, Novosibirsk, Russian Federation* * Corresponding author.

The strong connection between cancer-related inflammation and tumour development with pattern – recognizing receptors (PRRs) activation results in identification of new target molecules that could lead to improved cancer diagnosis and treatment. TLR3, RIG1 and MDA5 synthetic ligand poly(I:C) was shown to trigger apoptosis in cancer cells. However, TLR3 signaling also includes NF-kB transcription factor which has emerged as endogenous tumour promoter via stimulation of pro-inflammatory tumour microenvironment, enhancement of angiogenesis, tumour cell proliferation and metastasis. Thus down regulation of NF-kB-mediated effects after TLR3 activation is needed for implementation of TLR3 ligand-based therapy into clinical trials.

We have earlier demonstrated that DNA and sequence specific ODNs inhibit poly(I:C)-induced production of pro-inflammatory cytokines in human primary fibroblasts and endothelial cells (Cherepanova et al., Immunobiology, 2013). Using these specific ODNs and affinity modification/isolation approach combined with subsequent MALDI-TOF the main cellular targets for these ODNs were identified as Ku protein – heterodimer of KU70 and KU80 (Cherepanova et al., Exp. Opin. Biol. Ther., 2012).

The goals of this study are to reveal whether the ODNs target poly(I:C)-induced activation in tumour cells: cervical carcinoma (Hela) and epidermoid carcinoma (A431) and to confirm Ku

protein involvement in the observed effect. Poly(I:C) was shown to activate IL-6 production in Hela and A431 cells, and specific ODNs inhibit this activation with comparable efficacy as in primary cells. ODNs decrease both IL-6 concentration and mRNA expression rate in poly(I:C)-activated cells, indicating that NF-kB activation is also impaired.

To reveal whether Ku protein is involved in the inhibiting effect of ODNs, Ku70 level in Hela cells was reduced by siRNA, which were shown to inhibit the expression of Ku70 by up to 70%. Inhibiting efficacy of ODN is almost twice lower in Ku70 knock-down cells as compared to control siRNA, indicating that ODN binding to Ku protein is important for the inhibition. Whether Ku is directly involved in nucleic acid pattern recognition or have auxiliary functions, mediating ODN localization or poly(I:C)-proteins interactions, remains to be investigated. Nevertheless, efficient NF-kB pathway targeting by specific ODNs may improve dsRNA-based cancer therapy.

http://dx.doi.org/10.1016/j.ejcsup.2015.08.018

P132

Inflammation, immune disorders and cell destruction at the local level in patients with choroidal melanoma

M. Chernyavskaya[a,*], V. Chernych[a], A. Efremov[b], V. Atamanov[a]. [a] *FSBI "The Acad. S.N. Fyodorov Eye Microsurgery Complex" of the Minpubhealth of Russia, Novosibirsk Branch, Russian Federation,* [b] *Novosibirsk State Medical University, Department of Pathophysiology, Novosibirsk, Russian Federation* * Corresponding author.

Purpose: To research the characteristics of the inflammation immune disorders and cell destruction at the local level in the lacrimal and intraocular liquids in patients with choroidal melanoma.
Materials and methods: Investigation of concentration of the cytokines interleukin (IL) IL-4, IL-6, IL-8, IL-10, autoantibodies to antigens of native DNA (AAB to Ag of nDNA) in the lacrimal and intraocular liquids was performed in 36 patients (72 eyes) aged 34–83 years. The mean age of the study group patients was 60.45 years (15 males and 21 females). As standard indicators, survey results of 20 "healthy" donor lacrimal liquid – volunteers were used. For statistical data processing, descriptive statistics and methods of inter-group comparisons were used. Quantitative characteristics are presented as the median (25, 75 percentile). For comparison of quantitative traits, regression analysis was used. *P* value of <0.05 considered significant (95% confidence interval). Statistical analysis was performed using the software R (Team RC, 2013).
Results: A significant positive relation of concentration of IL-4, IL-6, IL-8, IL-10, AAB to Ag of nDNA in lacrimal liquid of eye with choroidal melanoma and paired "healthy" eye was reveled ($p < 0.05$). Concentrations of IL-6, IL-8, IL-10 and AAB to Ag of nDNA in the lacrimal liquid of the eye with choroidal melanoma were significantly higher as compared with the levels of the control group ($p < 0.05$). The level concentration of IL-4 in lacrimal liquid in eye with choroidal melanoma was significantly low ($p < 0.05$). The level concentration of IL-6 was significantly higher in the early (T1–T2) than in the later stages (T3–T4) of choroidal melanoma development ($p < 0.05$). All stages of choroidal melanoma were characterized by higher level of IL-6, compared with the control group ($p < 0.05$). Given the role of IL-6 in the pathogenesis of malignant diseases, the activity may be indicative of tumor progression in the early stages of development of choroidal melanoma. A significant increase in IL-10 was shown at stages T1 and T4 compared with the control group ($p < 0.05$). Regression analysis revealed a significant positive relation of concentration of IL-4, IL-6, IL-8, IL-10, AAB to Ag of nDNA between lacrimal liquid and intraocular liquids of the eye with choroidal melanoma ($p < 0.05$).IL-4 $r = 0{,}84$ (0.58; 1.47), $p < 0.05$ IL-6 $r = 0.98$ (0.64; 1.32), $p < 0.01$ IL-8 $r = 0.82$ (0.12; 1.73), $p = 0.05$ IL-10 $r = 0.84$ (0.01; 1.81), $p = 0.05$AAB to Ag of nDNA $r = 0.79$ (0.36; 1.25), $p < 0.05$.
Conclusions:

1.It was established that in the pathogenesis of choroidal melanoma, local Inflammation plays an important role as evidenced by a significant high concentration of IL-6, IL-8 due to lower levels of IL-4 and expressed immune disorders, cell destruction, as evidenced by significantly high level of AAB to Ag of nDNA, compared with the control group.
2.Use of lacrimal liquid is suitable for the study of the inflammation, immune disorders and cell destruction at the local level in patients with choroidal melanoma.
3.Significant increase in IL-6 level in lacrimal liquid was observed for all stages of choroidal melanoma, however, it was more pronounced in early stages (T1–T2), than in later stages (T3–T4).
4.A significant increase in IL-10 may indicate the severity of the local immunosuppression induced by tumor growth in the mechanisms of choroidal melanoma. A significant positive relationship between the concentrations of IL-4, IL-6, IL-8, IL-10, AAB to Ag of nDNA in the lacrimal liquids of eye and paired "healthy" eye was found in patients with choroidal melanoma.

http://dx.doi.org/10.1016/j.ejcsup.2015.08.019

A129

Analysis of Igf axis in development of HCC

N. Dashenkova*, A. Mikaelyan. *Russian Academy of Sciences Koltzov Institute of developmental biology, Moscow, Russian Federation* * Corresponding author.

Abstract: IGF signaling pathway plays an important role in the regulation of cell growth, proliferation, differentiation, apoptosis and survival. Deregulation of this pathway has been frequently identified in the development of hepatocellular carcinoma (HCC). IGF signaling pathway consists of IGF ligands (IGF-I and IGF-II), IGF binding proteins (IGFBP 1-7), and membrane-bound IGF receptors (IGF-1R, IGF-II/M6PR, and IGF-2R). The insulin-like growth factor binding proteins (IGFBPs) have several functions, such as IGF transporting, accumulation of IGF at the specific cell pools, inhibition and activation of ligand–receptor interaction. Furthermore, the Igfbps may act independently of IGF-pathway.